File No. 4988900-0010
Express Mail Label No. EU625636307US

Attorney Docket No.: 4988900-0001
Express Mail Label N . ET023669601US

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 C.F.R. §1.63)		)	First Named Inventor: Thomas P. Abbott
		)	Application Number:
X	Declaration Submitted With Initial Filing	☐ Declaration Submitted After Initial Filing	) Filing Date: Filed Herewith
			) Group Art Unit:
			) Examiner Name:

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

3-Methoxybenzyl Thiourea Derivatives and Improved Lipid Compositions Containing Same

(Title of Invention)

the specification of which:

(x) is attached hereto, or

( ) was filed by an authorized person on my behalf on _____ (Date)
as United States Application Number _____
or PCT International Application Number _____
and was amended on _____ (Date) (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below, and I have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application, on this invention filed by me or my legal representatives or assigns and having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached Yes	No
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Provisional Application Number(s)	Provisional Application Filing Date
60/202,562	May 10, 2000

☐ Additional provisional application numbers are listed on a supplemental priority data sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code, §120, of any prior United States application(s), or under §365(c) of any PCT international application(s) designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Prior U.S. Application Number	Prior PCT International Application Number	Filing Date of U.S. or PCT International Application	Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioners, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, and request that all correspondence and telephone calls in respect to this application be directed to LORD, BISSELL & BROOK, 115 South LaSalle Street, Chicago, Illinois 60603, Telephone No. (312) 443-0261, Facsimile No. (312) 443-0336:

Registered Practitioner	Registration Number
Keith D. Parr	33,322
Paul J. Molino	45,350
Scott B. Feder	33,129
Roberta Hastreiter	32,990

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity or enforceability of the application or any patent issued thereon.

Full name of sole or one joint inventor: Thomas P. Abbott
(Given names first, with Family name last)

Inventor's signature: _____

Date: _____

Residence: 2016 N. Delray St.
Peoria, Illinois 61614
(City and State for U.S. Residents;
City and Country for others)

Post Office Address: _____

Citizenship: U.S.A.

Full name of sole or one joint inventor: Alan Wohlman
(Given names first, with Family name last)

Inventor's signature: _____

Date: March 30, 2001

Residence: 2430 Cobblewood Drive
Northbrook, Illinois 60062
(City and State for U.S. Residents;
City and Country for others)

Post Office Address: _____

_____

Citizenship: U.S.A.

Declaration

Attorney Docket No. 4988900-0001

Supplemental Data Priority Sheet

☐ Additional foreign application numbers:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached Yes	No
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☐ Additional provisional application numbers:

Provisional Application Number(s)	Provisional Application Filing Date

☐ Additional U.S. or PCT international application numbers:

Prior U.S. Application Number	Prior PCT International Application Number	Filing Date of U.S. or PCT International Application	Patent Number (if applicable)

File No. 4988900-0010
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	DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 C.F.R. §1.63)		First Named Inventor: Thomas P. Abbott
			Application Number:
X	Declaration Submitted With Initial Filing	☐ Declaration Submitted After Initial Filing	Filing Date: Filed Herewith
			Group Art Unit:
			Examiner Name:

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

3-Methoxybenzyl Thiourea Derivatives and Improved Lipid Compositions Containing Same

(Title of Invention)

the specification of which:

(x) is attached hereto, or

( ) was filed by an authorized person on my behalf on _____ (Date)
as United States Application Number _____
or PCT International Application Number _____
and was amended on _____ (Date) (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below, and I have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application, on this invention filed by me or my legal representatives or assigns and having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached Yes	No
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I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

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I hereby claim the benefit under Title 35, United States Code, §120, of any prior United States application(s), or under §365(c) of any PCT international application(s) designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information known by me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

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As a named inventor, I hereby appoint the following registered practitioners, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, and request that all correspondence and telephone calls in respect to this application be directed to LORD, BISSELL & BROOK, 115 South LaSalle Street, Chicago, Illinois 60603, Telephone No. (312) 443-0261, Facsimile No. (312) 443-0336:

Registered Practitioner	Registration Number		
Keith D. Parr	33,322	Curtis P. Ribando	27,976
Paul J. Molino	45,350	M. Howard Silverstein	22,699
Scott B. Feder	33,129	John D. Fado	27,876
Roberta Hastreiter	32,990		

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity or enforceability of the application or any patent issued thereon.

Declaration

Attorney Docket No. 4988900-0001

Full name of sole or one joint inventor:	Thomas P. Abbott (Given names first, with Family name last)
Inventor's signature:	Thomas P. Abbott
Date:	3/30/01
Residence:	2016 N. Delray St. Peoria, Illinois 61614 (City and State for U.S. Residents; City and Country for others)
Post Office Address:	
Citizenship:	U.S.A.
Full name of sole or one joint inventor:	Alan Wohlman (Given names first, with Family name last)
Inventor's signature:	
Date:	
Residence:	2430 Cobblewood Drive Northbrook, Illinois 60062 (City and State for U.S. Residents; City and Country for others)
Post Office Address:	
Citizenship:	U.S.A.

Declaration

Attorney Docket No. 4988900-0001

Supplemental Data Priority Sheet

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☐ Additional provisional application numbers:

Provisional Application Number(s)	Provisional Application Filing Date

☐ Additional U.S. or PCT international application numbers:

Prior U.S. Application Number	Prior PCT International Application Number	Filing Date of U.S. or PCT International Application	Patent Number (if applicable)

PATENT
ATTORNEY DOCKET
NO. 4988900-0010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomas P. Abbott et al.

Filed: Herewith

Title: 3-Methoxybenzyl Thiourea Derivatives and Improved Lipid Compositions Containing Same

Group Art Unit:

Examiner:

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number
EU625636307US

Date of Deposit: August 1, 2003
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to Director of the United States Patent and Trademark Office, Attention: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Roberta L. Hastreiter
(Typed or printed name of person mailing)

Roberta L. Hastreiter
(Signature of person mailing)

DECLARATION OF THOMAS P. ABBOTT FILED UNDER 37 C.F.R. §1.132

THOMAS P. ABBOTT declares as follows:

1. I received a B.S. is chemistry at the University of Akron in Akron, Ohio, in 1964. Completing a thesis entitled, "Complexes of Styrene with Maleic Anhydride, Fumaronitrile and Methyl Methacrylate," I received a M.S. in polymer chemistry at the University of Akron in 1968. Completing a thesis entitled, "Reactivity of Methyl Methacrylate Units in Copolymers," I received a Ph.D. in polymer chemistry at the University of Akron, Institute of Polymer Science, in 1972.

2. From 1964 to 1969, I was a research chemist for Gencorp Corporate Research in Akron, Ohio, and was responsible for the identification and analysis of in-house research and production problems and competitive products. From 1971 to 1995, I was a research chemist for the National Center for Agricultural Utilization Research, United States Department of Agriculture, in Peoria, Illinois, and performed research on natural products (lignin, starch, gums, protein, bioactive plant components, etc.) to develop new products and unique processes. From 1995 to 2001, I was a research leader in the New Crops and Processing Research Unit of the National Center for Agricultural Utilization Research, United States Department of Agriculture, in Peoria, Illinois, and directed ten Ph.D. researchers and twenty-six staff members in agricultural products and processing research, and in natural products research, under a budget of 2.6 million dollars. I am currently the sole proprietor of a company named "Value-added Products from Nature," which is registered in the state of Washington.

3. I was a member of the American Oil Chemists Society from 1993 to 2001, and was a board member of the IOP division of this society in 1999. I was also a member of the American Chemical Society from 1971 to 2000, the president of the Association for the Advancement for Industrial Crops from 1996 to 1997, and the president of the American Kenaf Society in 2000. I am currently a member of the Association for the Advancement of Industrial Crops, and of the American Kenaf Society.

4. During my professional career, I have been an author of, or a named inventor on, more than one hundred publications or patents, respectively, including the following publications discussing antioxidants:

(a) Isbell, T.A., Abbott, T.P., and Carlson, K.D., "Oxidative Stability Index of Vegetable Oils in Binary Mixtures with Meadowfoam Oil," Ind. Crops Prod 9, 115-123 (1999);

(b) Abbott, T.P., Wohlman, A., and Momany, F.A., "Antioxidant from Meadowfoam Stabilizes other Oils," Abstracts of the 2000 AAIC Meeting, October 15-17, 2000, St. Louis, MO, Page 28; and

(c) Abbott, T.P., Wohlman, A., Isbell, T.A., Momany, F.A., Cantrell, C., Garlock, D.V., and Weisleder, D., "1,3-di(3-Methoxybenzyl) Thiourea and Related Lipid Antioxidants," Ind. Crops. Prod. 16:43-58 (2002).

5. I have extensive knowledge about chemistry, and about thiourea compounds.

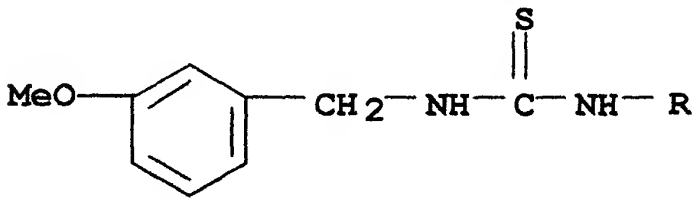
6. I am one of the two inventors of the invention described in the above-identified continuation application (hereinafter "the continuation application"), along with Alan Wohlman (hereinafter "the inventors").

7. I am informed that, in an official action dated September 9, 2002, for parent patent application U.S. Serial No. 09/840,768, filed on April 23, 2001 (hereinafter "the parent patent application"), the examiner at the U.S. Patent and Trademark Office rejected claims 1, 4, 7-9 and 10 of the application under 35 U.S.C. §103(a) as being unpatentable over Johns et al., Journal of Ethnopharmacology 5, 149-161, 1982 (hereinafter "the Johns et al. reference").

8. I have reviewed the Johns et al. reference in its entirety.

9. For the following reasons, it is my opinion as an expert in the area of thiourea compounds that the Johns et al. reference is not in the field of the inventors' endeavor (the use of 1-(3-methoxybenzyl)-3-substituted thiourea compounds for enhancing the oxidative stability of lipid and/or oil compositions), and is not reasonably pertinent to the particular problem with which the inventors were concerned (increasing the oxidative stability of lipid and oil compositions).

Rejected claim 1 of the application, as it has been amended in the accompanying Preliminary Amendment, describes a compound of the formula:



wherein R is a C_1 - C_{20} linear or branched alkyl, a C_6 - C_7 aryl, a hydroxy-substituted C_6 - C_7 aryl or an alkoxy-substituted C_6 - C_7 aryl, and wherein the compound enhances the oxidative stability of a lipid or oil to which the compound is added, with the proviso that R is not phenyl. Rejected claims 4, 7-9 and 10 of the application are dependent upon claim 1.

First, out of the thirteen pages contained in the Johns et al. reference, the only compound discussed therein that has any similarity to the compounds described by claims 1, 4, 7-9 and 10 of the application is the 1,3-di(4-methoxybenzyl)thiourea compound shown and described on page 152 of the reference. As is discussed in detail hereinbelow, this 1,3-di(4-methoxybenzyl)thiourea compound has a different chemical structure, and different chemical properties, in comparison with 1,3-di(3-methoxybenzyl) thiourea, the compound encompassed within the rejected claims that is the most similar to it.

Second, the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. In contrast with the rejected claims of the application, which describe 1-(3-methoxybenzyl)-3-substituted thiourea compounds that enhance the oxidative stability of lipids or oils to which the compounds are added, the Johns et al. reference describes the testing of pure isothiocyanates and plant extracts of *Tropaeolum tuberosum* for effects on the male and female reproductive processes, and for antibiotic activities and nematocial activities (being destructive to soil nematodes, such as roundworms and threadworms). For example, the Johns reference makes the following statements at the locations indicated:

Summary (page 149):

"The putative anti-aphrodisiac activity of *T. tuberosum* was examined in male rats fed a diet containing tubers of this taxon. Experimental animals and controls showed equal capability in impregnating females, although animals fed *T. tuberosum* showed a 45% drop in their blood levels of testosterone/dihydrotestosterone. This decrease appears to be related to the presence of isothiocyanates in the tubers. Feeding studies of female guinea pigs and *in vitro* studies to test the 17ß-estradiol binding inhibition of plant extracts and of pure isothiocyanates failed to substantiate any estrogenic activity of these taxa. However, preliminary results suggest that N,N-di-(methoxy-4-benzyl)thiourea competitively inhibits estradiol binding and may have estrogenic activity.

The antibiotic, insecticidal, nematocidal and diuretic properties of isothiocyanates substantiate several of the uses of *T. tuberosum* in Andean folk medicine." (Emphasis added.)

Page 150, Second Paragraph:

"Although magical beliefs accompany these accounts, the use of *T. tuberosum* in affecting human reproductive potential has continued to the present. . . Men refuse to eat these tubers because they believe that to do so produces impotence and an incapacity to have children. . . In modern Bolivia *T. tuberosum* is believed to induce menstruation . . . In folk medicine generally, menstruation is seen as a sign of femininity and fertility . . . and efforts are made using herbs and other means to induce late menstrual periods.

. . . Thus the folk uses of *Tropaeolum* spp. as female fertility agents and male antagonists have a certain logic to them." (Emphasis added.)

It is clear from the quotations of the Johns et al. reference set forth above, and from a reading of the remainder of the Johns et al. reference, that the problems that the authors of the Johns et al. reference were attempting to solve are completely different from the problem with which the inventors of the invention described in the rejected claims of the continuation patent application were concerned.

10. For the following reasons, it is also my opinion as an expert in the area of thiourea compounds that significant differences exist between the teachings and suggestions contained in the Johns et al. reference and the invention described in rejected claims 1, 4, 7-9 and 10 of the patent application.

First, each of rejected claims 1, 4, 7-9 and 10 of the patent application, as amended in the accompanying Preliminary Amendment, contains the phrase, "wherein the compound enhances the oxidative stability of a lipid or oil to which the compound is added." As is discussed hereinabove, the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds.

Second, the only compound described by the Johns et al. reference in its thirteen pages that has any similarity to the compounds described in the rejected claims is 1,3-di(4-methoxybenzyl)thiourea. The compound encompassed within the rejected claims that is the most similar to 1,3-di(4-methoxybenzyl)thiourea is 1,3-di(3-methoxybenzyl) thiourea.

1,3-di(3-methoxybenzyl) thiourea differs from 1,3-di(4-methoxybenzyl)-thiourea both structurally, and in its chemical properties.

1,3-di(3-methoxybenzyl) thiourea differs from 1,3-di(4-methoxybenzyl)-thiourea structurally in that 1,3-di(3-methoxybenzyl) thiourea has the methoxy group present on its two benzene rings in the meta position, whereas 1,3-di(4-methoxybenzyl)-thiourea has the methoxy group present on its benzene rings in the para position. As is discussed in detail below, this structural difference between these two compounds results in these compounds having different chemical properties. Most significant in connection with the rejected claims of the patent application is that, in comparison with 1,3-di(3-methoxybenzyl) thiourea, 1,3-di(4-methoxybenzyl)thiourea is significantly less soluble in lipids and oils and, as a result, has a significantly decreased ability to enhance the oxidative stability of a lipid or oil to which the compound is added.

The less soluble a substituted thiourea compound is in a lipid or oil to which the compound is added, the less the compound will have the ability to enhance the oxidative stability of the lipid or oil (because more of it remains in an undissolved state).

I conducted the experiments described below in order to compare the solubility of 1,3-di(4-methoxybenzyl)thiourea and 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil. From these experiments, it can be seen that the solubility of 1,3-di(4-methoxybenzyl) thiourea in refined meadowfoam seed oil is, at most, 25% (one fourth) of the solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil, and is probably less. Thus, 1,3-di(3-methoxybenzyl) thiourea is three times more effective as an agent to enhance the oxidative stability of a lipid or an oil to which it is added in comparison with 1,3-di(4-methoxybenzyl)thiourea.

Experiment No. 1 – Solubility of 1,3-di(4-methoxybenzyl)-thiourea in Refined Meadowfoam Seed Oil

1,3-di(4-methoxybenzyl) thiourea, 0.219 g, from a batch designated as 110202A, was added to 90.07 g of refined meadowfoam seed oil (Fancor lot CW6203). The mixture was heated to 50°C for 4 hours in a constant temperature bath. It was then filtered through Whatman #1 filter paper and then the filtrate was rinsed 3 times with 20 ml of hexane (Aldrich HPLC grade) to remove oil. The resulting undissolved crystals were dried in a hood and then removed from the filter paper and weighed. The sample of 1,3-di(4-methoxybenzyl) thiourea recovered was 0.151 g, which was 68.9% of that added to the refined meadowfoam seed oil. Solubility of the 1,3-di(4-methoxybenzyl) thiourea was calculated to be 680 mg/liter as a maximum because both recovery limitations and solubility in hexane wash would contribute to a higher solubility number, rather than to a lower solubility number.

The solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil is 3517 mg/liter, as is published in the literature (T.P. Abbott et al., "1,3-di(3-Methoxybenzyl) Thiourea and Related Lipid Antioxidants," Ind. Crops. Prod. 16:43-58 (2002)).

The results of this experiment showed that the solubility of 1,3-di(4-methoxybenzyl) thiourea in refined meadowfoam seed oil (690 mg/liter) is about 19.3% of the solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil (3517 mg/liter).

Experiment No. 2 – Solubility of 1,3-di(4-methoxybenzyl)-thiourea in Refined Meadowfoam Oil

In this experiment, I dissolved as much 1,3-di(4-methoxybenzyl) thiourea as possible in refined meadowfoam seed oil at 50°C, and then filtered off the excess. I sent the refined meadowfoam seed oil containing 1,3-di(4-methoxybenzyl) thiourea to another laboratory to be analyzed for sulfur content. It was determined that the sulfur content of the oil was <0.01%.

When a sulfur content of <0.01% in an oil is converted to a percent of antioxidant dissolved in the oil, it converts to <888 mg/liter of refined meadowfoam seed oil, or 25.2% of the published solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil (3517 mg/liter).

Although the results described above concern the solubility of 1,3-di(3-methoxybenzyl) thiourea and 1,3-di(4-methoxybenzyl) compounds in refined meadowfoam seed oil, similar results would be expected to occur with other types of lipids and oils.

11. For the following reasons, it is also my opinion as an expert in the area of thiourea compounds that the Johns et al. reference would not have suggested that the invention described in rejected claims 1, 4, 7-9 and 10 of the application, as amended in the accompanying Preliminary Amendment, would have a reasonable likelihood of success. As is discussed hereinabove, the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. Further, the only compound described by the Johns et al. reference in its thirteen pages that has any similarity to the compounds described in the rejected claims is 1,3-di(4-methoxybenzyl)thiourea. However, experiments that I performed (described hereinabove) show that 1,3-di(4-methoxybenzyl)-thiourea is not very soluble in lipids and oils and, thus, is not effective as an agent to enhance the oxidative stability of a lipid or an oil to which the compound is added. Thus, the Johns et al. reference would not have suggested that the compounds described by rejected claims 1, 4, 7-9 and 10 of the application would have a reasonable likelihood of

success in enhancing the oxidative stability of lipids or oils to which the compounds are added.

12. I am informed that, in an official action dated September 9, 2002, the examiner at the U.S. Patent and Trademark Office rejected claims 1, 2 and 5 of the parent patent application under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 3,949,089 of Maxwell et al. (hereinafter "the '089 patent").

13. I have reviewed the '089 patent in its entirety.

14. For the following reasons, it is my opinion as an expert in the area of thiourea compounds that the '089 patent is not in the field of the inventors' endeavor (the use of 1-(3-methoxybenzyl)-3-substituted thiourea compounds for enhancing the oxidative stability of lipid and/or oil compositions), and that the '089 patent is not reasonably pertinent to the particular problem with which the inventors were concerned (increasing the oxidative stability of lipid and oil compositions).

Rejected claim 1 of the application, as amended in the accompanying Preliminary Amendment, is set forth hereinabove. Rejected claims 2 and 5 of the application are dependent upon claim 1.

First, the only compound discussed in the '089 patent that has any similarity to the compounds described by claims 1, 2 or 5 of the application is the N-p-methoxybenzyl-N'-methylthiourea compound described in column 4 (EXAMPLE 1). As is described in detail hereinbelow, this N-p-methoxybenzyl-N'-methylthiourea compound, however, is structurally different from the compounds encompassed within claims 1, 2 and 5 of the application. Further, it is being used as an intermediate in the production of a guanidine hydriodide compound, and not as an antioxidant.

Second, the '089 patent does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. In contrast with the rejected claims of the application, which describe 1-(3-methoxybenzyl)-3-substituted thiourea compounds that enhance the

oxidative stability of lipids or oils to which the compounds are added, the '089 patent describes acid addition salts of N-p-methylbenzyl-N',N"-dimethylguanidine and of N-p-methoxybenzyl-N',N"-dimethylguanidine that are stated to have antiarrhythmic properties, and to be useful as antifibrillatory agents. For example, the '089 patent makes the following statements about the compounds described therein at the locations indicated:

Column 1, Lines 20-32:

"It has now been found that certain N-benzyl-N',N"-dimethylguanidine acid addition salts, namely the N-p-methylbenzyl- and N-p-methoxybenzyl-N',N"-dimethylguanidine acid addition salts possess unexpected advantages over that drug in the treatment of arrhythmia. These compounds not only have antiarrhythmic properties comparable to bethanidine, but also significantly less sympathetic blocking action, thus making possible the treatment of heart disorders with little or no adverse effect on blood pressure.

Among the types of arrhythmias which the compounds of this invention are effective in suppressing are ventricular fibrillations and atrial fibrillations. It has been found that an effective amount of the compounds, which are most desirably pharmacologically and pharmaceutically acceptable salts according to this invention, may be used to treat and suppress ventricular and atrial fibrillations in mammals, such as humans, dogs, cats and the like." (Emphasis added.)

Claim 7:

"A method of suppressing ventricular or atrial fibrillations in a mammal having a heart disorder which comprises administering to said mammal an effective ventricular or atrial fibrillation suppression amount of a pharmaceutically acceptable acid addition salt of N-p-methoxybenzyl-N'N"-dimethylguanidine." (Emphasis added.)

It is clear from the above quotations of the '089 patent, and from a reading of the remainder of this patent, that the problems that the inventors of the invention described in the '089 patent were attempting to solve are completely different from the problem with which the inventors of the invention described in the rejected claims of the present patent application were concerned.

15. For the reasons set forth hereinabove, it is also my opinion as an expert in the area of thiourea compounds that significant differences exist between the teachings and suggestions contained in the '089 patent and the invention described in rejected claims 1, 2 and 5 of the patent application, and that one skilled in the art would not look to guanidine compounds for structural guidance in the production of unique thiourea compounds.

In contrast with the rejected claims of the application, the '089 patent describes acid addition salts of N-p-methylbenzyl-N',N''-dimethylguanidine and N-p-methoxybenzyl-N',N''-dimethylguanidine, which are stated to be useful as antifibrillatory agents. The '089 patent also describes methods for treating cardiac arrhythmia with the use of these compounds.

For the following reasons, in my opinion, the chemical structures of, methods for synthesis, properties and uses of guanidine compounds, which are described in the '089 patent, and thiourea compounds, which are described in the rejected claims of the present application, are unrelated.

Guanidine compounds have a nitrogen atom double bonded to a carbon atom, whereas thiourea compounds have a sulfur atom double bonded to a carbon atom. Further, guanidine compounds have an additional hydrogen substituent, and the thiourea sulfur atom is not hydrogen substituted.

Further, unlike thiourea compounds, which are not especially basic, or even salt-forming, guanidine compounds are among the most basic of organic compounds. Recent publications concerning guanidine compounds are often related to the production of organic super-bases.

Moreover, uses for guanidine compounds, and/or derivatives or salts thereof, include rubber-curing acceleration and use as antifibrillatory agents for the treatment of cardiac arrhythmia. In contrast, thiourea compounds, and their organic derivatives and salts, are used as antioxidant agents, and for the recovering of metal.

In the organic chemistry textbook An Introduction to Organic Chemistry, A. Lowy and B. Harrow (Wiley and Sons, NY, NY (1961)), which was written on the basis of related compound structures, guanidine compounds are located in the chapter describing acid amides, whereas thiourea compounds are located in the chapter describing organosulfur compounds. I have enclosed a copy of the front cover of this textbook, as well as copies of pages 130-131 and 138-139 thereof (from chapter 11), which show the structure, and describe the properties, of guanidine in connection with a discussion of acid amides, and copies of pages 214-215 and 218-219 thereof (from chapter 18), which show the structure of thiourea, and describes it as being the sulfur analog of urea, in connection with a discussion of organosulfur compounds.

In a different organic chemistry textbook, Organic Chemistry, R.Q. Brewster and W. E. McEwen (Prentice-Hall, (1961)), guanidine compounds are described in the chapter describing carbonic acid derivatives, whereas thiourea compounds are described in the chapter describing aliphatic sulfur compounds. I have enclosed a copy of the front cover of this textbook, as well as a copy of page 260 thereof (from chapter 13), which shows the structure of guanidine in connection with a discussion of derivatives of carbonic acid, and page 318 thereof (from chapter 15), which contains a subsection on thioureas in connection with a discussion of aliphatic sulfur compounds.

Many modern organic chemistry textbooks, such as Advanced Organic Synthesis, M.B. Smith and J. March (Wiley-Interscience, NY, NY. 5th ed. (2001)), do not group compounds by related properties, but rather by compound synthesis methods or mechanisms of synthesis. Substituted thiourea compounds and guanidine compounds are not produced by the same methods. Thus, these two groups of compounds are generally located in different sections in connection with different methods of synthesis in these types of organic chemistry textbooks. I have enclosed a copy of the front cover of Advanced Organic Synthesis, as well as copies of pages 1190-1193 thereof, showing that

substituted thiourea compounds and guanidine compounds are located in different sections of this textbook.

I performed computer searches for publications describing guanidine compounds and thiourea compounds in the same article using: (a) the ArticlesFirst database of journal articles; (b) the WorldCat database of books; and (c) the Medline database of scientific publications. The ArticlesFirst database provided one reference in which both thiourea and guanidine were listed as reducing agents. The Medline database provided 2367 references for guanidine compounds, 2978 references for thiourea compounds, and no references describing thiourea compounds and guanidine compounds in the same article. The WorldCat database found hundreds of references for each class of compound separately, but only one publication (a thesis paper) describing the two classes of compounds together ("Investigation of Ammoniation and Ammonolysis Reactions by Pressure-composition Isotherms," W.R.M. Bride. Thesis, Austin, TX. 1955).

In view of the above, it is clear that the structure of a substituted guanidine compound effective for controlling cardiac arrhythmia does not suggest a substituted thiourea compound effective for enhancing the oxidative stability of oil or lipid compositions to those of skill in the art. A substituted guanidine compound does not imply that a similarly substituted thiourea compound would have similar or related properties, uses or methods for synthesis. Those of skill in the art would not look to substituted guanidine compounds for guidance regarding the properties of substituted thiourea compounds.

Further, the only compound described by the '089 patent that has any similarity to the compounds described in the rejected claims is N-p-methoxybenzyl-N'-methylthiourea. The compound encompassed within the rejected claims that is the most similar to N-p-methoxybenzyl-N'-methylthiourea is 1-(3-methoxybenzyl)-3-methyl-2-thiourea. 1-(3-methoxybenzyl)-3-methyl-2-thiourea differs from N-p-methoxybenzyl-N'-methylthiourea structurally, and likely in its chemical properties.

1-(3-methoxybenzyl)-3-methyl-2-thiourea differs from N-p-methoxybenzyl-N'-methylthiourea structurally in that the methoxybenzyl group present on the benzene ring is in the meta position, whereas N-p-methoxybenzyl-N'-methylthiourea has the

methoxy group present on its benzene rings in the para position. Based upon the experiments that are presented hereinabove in Section 10 of this Declaration, and which involve a similar set of circumstances, I would predict that the structural difference between these two compounds would result in these compounds having different chemical properties. Based upon these experiments, I would predict that N-p-methoxybenzyl-N'-methylthiourea, in comparison with 1-(3-methoxybenzyl)-3-methyl-2-thiourea, would be significantly less soluble in lipids and oils and, as a result, have a significantly decreased ability to enhance the oxidative stability of a lipid or oil to which the compound is added. Again, in the '089 patent, the N-p-methoxybenzyl-N'-methylthiourea compound is being used as an intermediate in the production of a guanidine hydriodide compound, and not as an antioxidant.

16. For the following reasons, it is also my opinion as an expert in the area of thiourea compounds that the '089 patent would not have suggested that the invention described in rejected claims 1, 2 and 5 of the application, as amended in the accompanying Preliminary Amendment, would have a reasonable likelihood of success. As is discussed hereinabove, the '089 patent does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. Further, the N-p-methoxybenzyl-N'-methylthiourea compound described in line 28, column 4, of the '089 patent is used only as an intermediate during the synthesis of a guanidine hydriodide compound (the final product described in Example 1 of the '089 patent). Thus, the '089 patent would not have suggested that the compounds described by rejected claims 1, 2 and 5 of the application would have a reasonable likelihood of success in enhancing the oxidative stability of lipids or oils to which the compounds are added.

14. All statements in the Declaration of my own knowledge are true and all statements made on information and belief are believed to be true. I am aware that willful false statements and the like are punishable by fine and imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patent issuing thereon.

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July 3, 2003
Date

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